REMARKS

Claims 22 and 23 have been cancelled and new claim 30 has been added. Claims 20, 21, 24 and 29 are pending. Applicants submit that the amendments are not new matter and are fully supported by the specification. Entry of the Amendment is respectfully requested. Applicants further request an interview with the Examiner, as Applicant believes that such an interview would expedite prosecution of this application. Furthermore, Applicant would like to thank the Examiner for agreeing to have such an interview after the Amendment and Response is filed.

Double Patenting

A terminal disclaimer accompanies this response, which Applicants believe overcome the rejections based on double patenting. The disclaimers are made to expedite issuance and are not intended as an admission that any claim of the claimed invention is the same or an obvious variant of those of U.S. Patent Nos. 6,238,892, 6,008,024, and 5,843,779. U.S. Patent No. 6,238,892 does not relate to a kit, as in the present claim 29, and therefore the claim 29 of the present application is patentably distinct from claims 1 and 2 of U.S. Patent No. 6,238,892. As to the double patenting objection involving U.S. Patent No. 5,843,779, claims 20, 24 and 29 as amended are patentably distinct from all the claims of U.S. Patent No. 5,843,779. The antibody AT120 binds a phosphatase insensitive epitope of tau as evidenced by the reactivity of AT120 with PHF-tau is not sensitive to a phosphatase treatment. See Vandermeeren et al. 1993, page 1829 (1993).

The Examiner has also requested that the Applicants inform her of other pending applications or issued patents drawn to the tau monoclonal antibodies. Currently there is one pending patent application Serial No. 09/790,148. This application, however, relates to tau monoclonal antibodies with the same characteristics as the AT120 monoclonal antibody which binds a phosphatase insensitive epitope of tau. Accordingly, the claims of the application under examination are patentably distinct from 09/790,148. Furthermore, there are two U.S. Patents on tau monoclonal antibodies, 6,121,003 and 6,238,892.

New Matter

Claim 22 was rejected by the Examiner under 35 U.S.C. § 112 first paragraph as containing new matter. Applicants respectfully traverse the rejection. However, to accelerate prosecution of this application, the cancellation of claim 22 and the amendment of claim 20 render this rejection moot.

Enablement

Claims 20-24 and 29 were rejected by the Examiner under 35 U.S.C. §112 first paragraph as not being enabled for a monoclonal antibody that forms an immunological complex with any phosphorylated epitope present in a human abnormally phosphorylated tau protein, variant peptides, or other phosphorylated epitopes," page 5, Office Action. Applicants respectfully traverse the rejection.

First, the specification is enabled for antibodies that have the recited functional properties. In Example 1, pages 18-21 of the specification, preparation of the monoclonal antibodies with the characteristics of AT8 are taught. Furthermore, AT8 has been deposited at ECACC under No. 91100806. AT8 has the functional properties contained in amended claim 20, including the following:

1. The specification teaches how to prepare human abnormally phosphorylated tau protein. Example 1, pages 18 and 19 of the specification.

2. AT8, by way of example, forms an immunological complex with abnormally phosphorylated protein. Example 2, pages 21 through 24 of the specification.

3. AT8, by way of example, forms an immunological complex with a phosphorylated epitope. As defined in the specification page 8, lines 3 through 5, phosphorylated epitope is defined as "an epitope that is destroyed when it is treated with phosphatase enzyme." Furthermore, the results in Figure 4, line 1 through 2 show that AT8 epitope is phosphatase sensitive.

4. Example 2 and Figure 2 of the specification teach that abnormally phosphorylated tau proteins that are recognized by AT8 have an apparent molecular weight which is higher than that of normal tau proteins.

5. The apparent molecular weight of abnormally phosphorylated tau proteins recognized by AT8 can be decreased to that of normal tau proteins upon treatment of the

abnormally phosphorylated tau protein with a dephosphorylating agent, Goedert et al., 5066 (1993).

6. AT8 does not form an immunological complex with "normal tau" as shown in the ELISA Example 2, pages 21 through 23 and Figure 1 of the specification and in the Western Blotting as shown in the Example 2, pages 23 through 24 and Figure 2 of the specification. The specification is directed towards the preparation of affinity purified normal/human tau (page 27, lines 6-30). The normal tau is used in experiments set forth in Example 2. Fetal tau and newborn rat tau, as referenced by the Examiner, are not picked up in this preparation method and therefore are not considered "normal tau." The preparation of normal/human tau includes a purification step with antibody BT2 (page 27, lines 19-23). The antibody BT2 recognizes a nonphosphorylated epitope identical to the Tau-1 epitope situated in the region of the AT8 epitope and only recognizing PHF after dephosphorylization. Because AT8 recognizes a phosphorylated epitope on fetal tau and on newborn rat tau, these will not be picked up by BT2. Therefore, fetal tau and newborn rat tau are not considered normal tau according to the specification of the present application.

7. AT8 does not form an immunological complex with tau protein derived from a human brain, the homogenates being isolated from a patient having died of a nonneurological disorder. AT8 does not detect normal human tau, as previously discussed.

8. AT8 does not form an immunological complex with a phosphorylated epitope treated with a dephosphorylating agent, as evidenced in Goedert et al., 5069 (1993).

AT8 further has the additional properties of claim 21. AT8 forms an immunological complex with YSS*PGS*PGT (SEQ ID NO 1) and/or YSSPGS*PGT (SEQ ID NO 2). Example 5 of the specification, pages 29-31 demonstrate that immunoblotting of peptides comprising YSS*PGS*PGT (SEQ ID NO 1) and modification of that peptide at S199 and/or S202 with AT8. Figure 4 of the specification shows that YSS*PGS*PGT (SEQ ID NO 1) or YSSPGS*PGT (SEQ ID NO 2) is needed for binding of AT8 to form an immunological complex with a peptide, which forms an immunological complex with a monoclonal antibody, which in turn forms a complex with YSS*PGS*PGT (SEQ ID NO 1) or YSSPGS*PGT (SEQ ID NO 2).

Apart from AT8, the specification also points to other abnormally phosphorylated epitopes on tau. As indicated at page 8, lines 34-35 of the specification, monoclonal antibodies of the invention include those which recognize a serines on tau in the phosphoserine form. Of the 441 amino acids making up the tau protein, only 45 are serine. Only 16 of these 45 serines are phosphorylated in abnormally phosphorylated tau. Accordingly, the number of epitopes as indicated in the specification, is limited and the number of claimed antibodies is narrow. Finally, numerous efforts have been made, as set forth in the specification, to obtain monoclonal antibodies that are specific for AD tau (PHF-tau) that do not recognize normal tau. This application is the first disclosure on PHF-tau specific monoclonal antibodies.

Indefiniteness

Claim 22 was rejected by the Examiner under 35 U.S.C. §112 as being indefinite in its limitations in (c) and (d). Applicants respectfully traverse this rejection. However, to expediate prosecution of this application, Applicants have cancelled claim 22 and amended claim 20, changing the language of (c) and deleting (d).

Section 102(b) Anticipation

Claims 20, 23 and 24 were rejected by the Examiner as being anticipated by Dickson. Applicants respectfully traverse this rejection. However, to expedite prosecution of this application. Applicants have amended claim 20. The amendment to claim 20 clearly distinguishes MP14 disclosed in Dickson from the monoclonal antibodies of the claimed invention.

First, Dickson discloses that MP14 does form an immunological complex with normal tau protein, Dickson et al., page 255, lines 20 through 24. In addition, MP14 forms an immunological complex with a phosphorylated epitope on abnormally phosphorylated tau treated with dephosphorylating agent. In other words, the staining of A68 by MP14 is not effected by phosphatase, Ksiezak-Reding et al., page 423, lines 18 through 20 (1990). Thus, MP14, as disclosed in Dickson et al., is in direct contrast with the features of the monoclonal antibodies in claim 20, as amended.

Section 102(e) Anticipation

Claims 20, 23 and 24 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,601,985 to Trojanowski. Claim 29 was rejected

by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Trojanowski as applied in claims 20, 23, and 24, and in further view of Dickson and Catty et al. Applicants respectfully traverse the rejections.

Unlike the claimed invention, Trojanowski discusses "T3P" which is an antiserum (column 10, lines 14 through 16), consisting of polyclonal antibodies (column 6, lines 64 through 65) and which recognizes many different epitopes. In contrast, the antibodies of the claimed invention are monoclonal and recognize one epitope.

For these same reasons, claim 29 is not anticipated by Trojanowski in view of Dickson and Catty. As previously discussed, T3P disclosed in Trojanowski is an antiserum. The MP14 monoclonal antibody disclosed in Dickson does not have the characteristics of the antibodies of claim 20. Accordingly, there is no monoclonal antibody available in the art that could be used in the ELISA, according to Catty to obtain the kit of claim 29.

Obviousness

Claims 20, 22, 23, and 24 were rejected under 35 U.S.C. § 103(a) as unpatentable over Lee in view of Goding. Applicants respectfully traverse this rejection. Lee discloses an antisera, "T3P", which recognizes A68, but does not recognize normal tau. According to the Examiner, it would be obvious to use the teaching of Lee and the conventional techniques of Goding to generate the monoclonal antibodies with the characteristics of the monoclonal antibodies of the claimed invention. However, one skilled in the art would not have been motivated to prepare monoclonal antibodies from Lee.

While Lee uses several monoclonal antibodies (page 677) for the labeling of A68 and tau, Lee does not obtain a monoclonal antibody with the characteristics of the monoclonal antibodies contained in claim 20, as amended. Because at least 7 monoclonal antibodies are disclosed in Lee, one skilled in the art would rather have been guided away from trying to obtain further monoclonal antibodies.

In addition, there is no motivation to combine these two references. The polyclonal antisera described in Lee were produced in rabbits while Goding indicates that for production of monoclonal antibodies the species of choice is limited to the mouse and/or rat (Goding, page 57, lines 12-13), preferably the mouse (Goding, page 57, lines

17-19). In fact, different publications show that the immune response can differ enormously in different animal species (Katsutani and Shionoya, 1992) and even within different strains of the same animal species (Aida et al., 1997a, 1997b; Hue et al. (1965)). Immunization with certain drugs, for example, gave a positive response in guinea pigs, while the same drug could not induce drug specific antibodies in mice (Katsutani and Shionoya, page 169, lines 15-19 and Table 6). Humoral response to TNBS and two ß-lactum antibiotics was totally different in three guinea pig strains. (Aida et al. 1997a, Abstract and Table 1; 1997b, Abstract and Tables 1 and 2). Quantitative differences in antibody responses between two strains of rabbits and between two strains of mice have also been reported. Accordingly, based on the polyclonal rabbit antiserum disclosed by Lee, one skilled in the art would have no reasonable expectation that the immunization of mice or rats would be successful.

Furthermore, even if an immune response would have been obtained in mice, this immune response would result in the production of a multitude of different antibodies, recognizing a multitude of different epitopes. There was, therefore, not any reasonable expectation that precisely the antibody which specifically recognizes the desired phosphatase sensitive epitope according to the claimed invention would be produced and even if it would be produced that the correct hybridoma would be picked up and the desired epitope would be retained within the cones obtained. In fact, according to Tijssen (1985, page 74, lines 21-27), during the production of monoclonal antibodies, the loss of chromosomes and the danger of overgrowth of the useful clones is significant and that only a small fraction may produce a specific antibody (page 75, lines 7-9). A significant number of these initially positive clones may ultimately be lost (page 77).

Claims 20, 21, 23, and 24 were further rejected under 35 U.S.C. § 103(a) as being unpatentable over Dickson in view of Kosik et al. and Binder et al. Applicants respectfully traverse this rejection.

First Dickson, as previously discussed, does not teach the monoclonal antibodies of the invention. Furthermore, it would not be obvious to prepare monoclonal antibodies with the characteristics of the claimed invention based on the teachings in Kosik and Binder. Monoclonal antibodies of the claimed invention have specific binding characteristics as disclosed in the amended claim 20. Furthermore, there is no suggestion

in the three documents cited by the Examiner to combine these references in order to arrive at the monoclonal antibodies of the claimed invention.

In the claimed invention, the preparation of a monoclonal antibody with specific binding characteristics is a sequential process done without a reasonable expectation that the antibody possessing the desired characteristics would be obtained. These steps include: (1) the selection of an immunogen, and (2) screening for monoclonal antibody with the desired characteristics.

1. Selection of the immunogen

Different kinds of antigens are available for use in the immunization protocol and a selection needed to be made. From the prior art documents indicated by the Examiner, it is not at all clear which immunogen should be used in order to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention:

- Binder et al. teaches the use of bovine MAP and bovine tau as an immunogen for the preparation of monoclonal antibodies. Binder et al. does not use Alzheimer basal forebrain, nor does it teach which antigen should be used in order to obtain the monoclonal antibodies of the invention that specifically recognize abnormally phosphoralated tau and that do not recognize normal tau.
- Similar to the antigen used in the claimed invention (tau protein isolated from AD brain), Dickson et al. indeed uses extracts from AD brain as an immunogen. However, Dickson et al. does not teach how to isolate these extracts from AD brain in order to obtain the immunogenicity needed to produce the monoclonal antibodies of the claimed invention. In fact, the monoclonal antibody (NP14) of Dickson et al. does not have the characteristics of the monoclonal antibodies of the claimed invention i.e., this monoclonal antibody also recognizes normal tau. Thus, Dickson et al. teaches the skilled person away from using extracts from AD brain as an immunogen since a monoclonal antibody with other characteristics was obtained. Nowhere, Dickson et al. does not disclose which antigen should be used in order to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the claimed invention.
- In Table 1 of Kosik et al., different monoclonal antibodies are shown as well as the immunogens used for their production: human and bovine MAPs, bovine tau,

detergent extracts of rat brain protein and Alzheimer basal forebrain. Kosik et al. does not indicate which of these antigens should be selected in order to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Kosik et al. shows that the use of an antigen (Alzheimer fatal basal forebrain) similar to the antigen used in the claimed invention (tau protein isolated from AD brain) as an immunogen leads to the isolation of a monoclonal antibody (Alz50) with characteristics different from characteristics of the monoclonal antibodies of the claimed invention. Accordingly, Kosik et al. teaches the skilled person away from using Alzheimer basal forebrain.

2. Screening for the monoclonal antibody with the desired characteristics

Different kinds of screening procedures are available for use in the selection of the hybridoma that secretes a monoclonal antibody with the desired characteristics. The present inventors selected a sandwich ELISA with polyclonal rabbit anti-human tau antibodies affinity purified with affinity purified human tau. None of the prior art documents indicated by the Examiner discloses this screening assay or a screening assay similar to this. Furthermore, these prior art documents do not teach that such a screening assay can be used to isolated a hybridoma producing a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention:

- As indicated by the Examiner, Binder et al. teaches the use of a competitive ELISA to measure the level of tau or microtubulin. Binder et al. does not teach that this competitive ELISA can be used to select a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Binder et al. do not teach which adaptation is needed in order to use this competitive ELISA in a screening assay to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Nowhere Binder et al. teaches the sandwich ELISA used in the method of the claimed invention or how to select between monoclonal antibodies in order to obtain the desired antibody. Binder et al. certainly does not teach how to select a monoclonal antibody with the characteristics of the monoclonal antibodies of the claimed invention.
- Dickson et al. are silent on the method for the screening for monoclonal antibodies with the desired characteristics.

- Kosik et al. teaches the epitope that is recognized by Tau-1 and which is phosphatase sensitive. Kosik et al. do not teach how this epitope could be used in a screening assay. In fact, the use of this epitope as such in a screening assay for monoclonal antibodies would not result in the selection of a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Kosik et al. do not teach how to obtain a phosphorylated epitope that could be used in the selection of a monoclonal antibody with the desired characteristics. Accordingly, the skilled person would not have any guidance where phosphorylation should occur in order to obtain an epitope recognized by the monoclonal antibodies of the claimed invention. In fact, Kosik et al. teaches away from obtaining a phosphorylated epitope since they point to the fact that this epitope does not contain any known kinase concensus sequence (page 820, left column, lines 48-50). In addition, the use of a peptide instead of a full protein could result in a different conformation of the epitope to be recognized. Accordingly, antibodies that would normally not be recognized might be selected, while other antibodies that should have been recognized might be missed. Therefore, by using the peptide as disclosed in Kosik et al., there was no reasonable expectation of success that the monoclonal antibodies of the claimed invention could be obtained.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claim 20 has been amended as follows:

20. (Amended) A monoclonal antibody which forms an immunological complex with a phosphorylated epitope present in a human abnormally phosphorylated tau protein, wherein said tau protein is obtained from a brain homogenate, isolated from the cerebral cortex of a patient having Alzheimer's disease or having died of Alzheimer's disease[.]; further wherein:

A. said abnormally phosphorylated tau proteins

i. present an apparent molecular weight which is higher than that of normal tau proteins, obtained from brain homogenates isolated from a patient having died of nonneurological disorders; and

ii. the apparent molecular weight can be decreased to that of normal tau proteins upon treatment of said abnormally phosphorylated tau proteins with a dephosphorylating agent; and

B. the monoclonal antibody is selected to exclude forming in the immunological complex with:

i. normal tau proteins;

ii. tau protein present in brain homogenates derived from the human brain, said homogenates being isolated from a patient having died of a nonneurological disorder; and

iii. the phosphorylated epitope that has been dephosphorylated with a dephosphorylating agent.

New claim 30 has been added.